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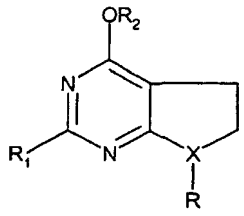
(54) Title: CORTICOTROPIN RELEASING FACTOR ANTAGONISTS



(I)

(57) Abstract: The present invention provides compounds of formula (I) including stereoisomers, prodrugs and pharmaceutically acceptable salts or solvates thereof, wherein R is aryl or heteroaryl and each of the above groups R may be substituted by 1 to 4 groups selected from: halogen, C1-C6 alkyl, C1-C6 alkoxy, halo C1-C6 alkyl, C2-C6 alkenyl, C2-C6 alkynyl, halo C1-C6 alkoxy, $-COR_4$, nitro, $-NR_3R_4$ cyano, or a group R_5; R_1 is hydrogen, C1-C6 alkyl, C2-C6 alkenyl, C2-C6 alkynyl, halo C1-C6 alkyl, halo C1-C6 alkoxy, halogen, NR_3R_4 or cyano; R_2 corresponds to a group CHR_6R_7; R_3 is hydrogen, C1-C6 alkyl; R_4 independently from R_3, has the same meanings; R_5 is C3-C7 cycloalkyl, which may contain one or more double bonds; aryl; or a 5-6 membered heterocycle; wherein each of the above groups R_5 may be substituted by one or more groups selected from: halogen, C1-C6 alkyl, C1-C6 alkoxy, halo C1-C6 alkyl, C2-C6 alkenyl, C2-C6 alkynyl, halo C1-C6 alkoxy, C1-C6 dialkylamino, nitro or cyano; R_6 is hydrogen, C2-C6 alkenyl or C1-C6 alkyl, wherein each of the above groups R_6 may be substituted by one or more groups selected from: C1-C6 alkoxy and hydroxy; R_7 independently from R_6, has the same meanings; X is carbon or nitrogen; to processes for their preparation, to pharmaceutical compositions containing them and to their use in the treatment of conditions mediated by corticotropin-releasing factor (CRF).

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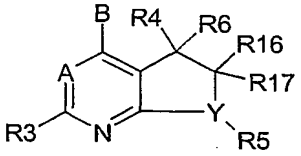
WO 95/33750 also describes compounds of general formula B having CRF antagonistic activity,



B

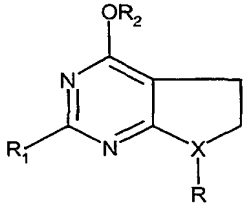
in which A and Y may be nitrogen and carbon and B may correspond to an ether derivative. There is no disclosure related to compounds corresponding to the above definition.

Due to the physiological significance of CRF, the development of biologically-active small molecules having significant CRF receptor binding activity and which are capable of antagonizing the CRF receptor remains a desirable goal. Such CRF receptor antagonists would be useful in the treatment of endocrine, psychiatric and neurologic conditions or illnesses, including stress-related disorders in general.

While significant strides have been made toward achieving CRF regulation through administration of CRF receptor antagonists, there remains a need in the art for effective small molecule CRF receptor antagonists. There is also a need for pharmaceutical compositions containing such CRF receptor antagonists, as well as methods relating to the use thereof to treat, for example, stress-related disorders. The present invention fulfills these needs, and provides other related advantages.

In particular the invention relates to novel compounds which are potent and specific antagonists of corticotropin-releasing factor (CRF) receptors.

The present invention provides compounds of formula (I) including stereoisomers, prodrugs and pharmaceutically acceptable salts or solvates thereof



(I)

wherein

R is aryl or heteroaryl and each of the above groups R may be substituted by 1 to 4 groups selected from:
halogen, C1-C6 alkyl, C1-C6 alkoxy, halo C1-C6 alkyl, C2-C6 alkenyl, C2-C6 alkynyl, halo C1-C6 alkoxy, $-COR_4$, nitro, $-NR_3R_4$ cyano, or a group R_5;

R_1 is hydrogen, C1-C6 alkyl, C2-C6 alkenyl, C2-C6 alkynyl, halo C1-C6 alkyl, halo C1-C6 alkoxy, halogen, NR_3R_4 or cyano;

R_2 corresponds to a group CHR_6R_7;

All such isomeric forms are included within the present invention, including mixtures thereof. Furthermore, some of the crystalline forms of the compounds of structure (I) may exist as polymorphs, which are included in the present invention.

The term C1-C6 alkyl as used herein as a group or a part of the group refers to a linear or branched alkyl group containing from 1 to 6 carbon atoms; examples of such groups include methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl, tert butyl, pentyl or hexyl.

The term C3-C7 cycloalkyl group means a non aromatic monocyclic hydrocarbon ring of 3 to 7 carbon atom such as, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl; while unsaturated cycloalkyls include cyclopentenyl and cyclohexenyl, and the like.

The term halogen refers to a fluorine, chlorine, bromine or iodine atom.

The term halo C1-C6 alkyl means an alkyl group having one or more carbon atoms and wherein at least one hydrogen atom is replaced with halogen such as for example a trifluoromethyl and the like.

The term C2-C6 alkenyl defines straight or branched chain hydrocarbon radicals containing one or more double bond and having from 2 to 6 carbon atoms such as, for example, ethenyl, 2-propenyl, 3-butenyl, 2-butenyl, 2-pentenyl, 3-pentenyl, 3-methyl-2-butenyl or 3-hexenyl and the like.

The term C1-C6 alkoxy group may be a linear or a branched chain alkoxy group, for example methoxy, ethoxy, propoxy, prop-2-oxy, butoxy, but-2-oxy or methylprop-2-oxy and the like.

The term halo C1-C6 alkoxy group may be a C1-C6 alkoxy group as defined before substituted with at least one halogen, preferably fluorine, such as difluoromethoxy, or trifluoromethoxy.

The term C2-C6 alkynyl defines straight or branched chain hydrocarbon radicals containing one or more triple bond and having from 2 to 6 carbon atoms including acetylenyl, propynyl, 1-butynyl, 1-pentynyl, 3-methyl-1-butynyl and the like.

The term aryl means an aromatic carbocyclic moiety such as phenyl, biphenyl or naphthyl.

The term heteroaryl means an aromatic heterocycle ring of 5-to 10 members and having at least one heteroatom selected from nitrogen, oxygen and sulfur, and containing at least 1 carbon atom, including both mono-and bicyclic ring systems.

Representative heteroaryls include (but are not limited to) furyl, benzofuranyl, thiophenyl, benzothiophenyl, pyrrolyl, indolyl, isoindolyl, azaindolyl, pyridyl, quinolinyl, isoquinolinyl,

Preferred compounds according to the invention are:
7-(2,4-dichlorophenyl)-4-(1-ethyl-propoxy)-2-methyl-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]-pyrimidine (1-1);
7-(2,4-dichlorophenyl)-4-(1-isopropyl-2-methyl-propoxy)-2-methyl-6,7-dihydro-5*H*-pyrrolo-[2,3-*d*]pyrimidine (1-2);
7-(2,4-dichlorophenyl)-4-(1-isopropyl-3-methyl-butoxy)-2-methyl-6,7-dihydro-5*H*-pyrrolo-[2,3-*d*]pyrimidine (1-3);
7-(2,4-dichlorophenyl)-4-(2-methoxy-1-methoxymethyl-ethoxy)-2-methyl-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidine (1-1-4);
7-(2,4-dichlorophenyl)-4-(2-ethyl-butoxy)-2-methyl-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]-pyrimidine (1-5);
7-(2,4-dichlorophenyl)-4-(2-ethoxy-1-ethoxymethyl-ethoxy)-2-methyl-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidine (1-6);
7-(2,4-bis-trifluoromethyl-phenyl)-4-(1-ethyl-propoxy)-2-methyl-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidine (1-7);
7-(2,4-dichlorophenyl)-4-(1-ethyl-2-methyl-allyloxy)-2-methyl-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidine (1-8);
7-(2,4-dichlorophenyl)-4-(1-methoxymethyl-propoxy)-2-methyl-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidine (1-9);
2-[7-(2,4-dichlorophenyl)-2-methyl-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-4-yloxy]butan-1-ol (1-10);
7-(2,4-bis-trifluoromethyl-phenyl)-4-(1-methoxymethyl-propoxy)-2-methyl-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidine (1-12);
4-[4-(1-ethyl-propoxy)-2-methyl-5,6-dihydro-pyrrolo[2,3-*d*]pyrimidin-7-yl]-3-trifluoromethyl-benzamide (1-13);
4-(1-ethyl-propoxy)-7-[2-(1-ethyl-propoxy)-6-trifluoromethyl-pyridin-3-yl]-2-methyl-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidine (1-14);
2-[4-(1-ethyl-propoxy)-2-methyl-5,6-dihydro-pyrrolo[2,3-*d*]pyrimidin-7-yl]-5-trifluoromethyl-benzonitrile (1-15).

In general, the compounds of structure (I) may be made according to the organic synthesis techniques known to those skilled in this field, as well as by the representative methods set forth in the Examples.

Compounds of formula (I), and salts and solvates thereof, may be prepared by the general methods outlined hereinafter. In the following description, the groups R, R_1, R_2, R_3, R_4, R_5, R_6, R_7 X and n have the meaning as previously defined for compounds of formula (I) unless otherwise stated.

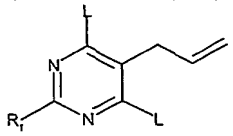
Compounds of formula (I), may be prepared by reaction of a compound of formula (II)

The oxidation is carried out with ozone at low temperature, e.g. –78°C, in a solvent such as dichloromethane.

The reduction takes places using for example sodium borohydride in a solvent such as alcohol.

Examples of suitable nitrogen protecting group include alkoxycarbonyl, e.g. t-butoxycarbonyl and arylsulphonyl, e.g phenylsulphonyl.

Compounds of formula (V) may be prepared by reaction of a compound of formula (VI), wherein L is defined as above, with amine (VII).



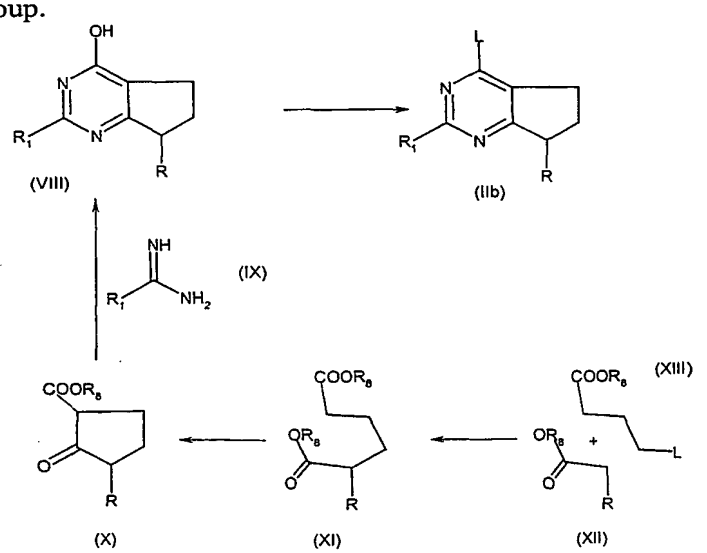
(VI)

H_2N-R (VII)

The reaction preferably takes place in an aprotic solvent such as tetrahydrofuran, dichlorometane or N,N-dimethyl formamide in the presence of a strong base such sodium hydride and with heating.

Compounds of formula (VI) and (VII) are either known compounds or may be prepared by analogous method to those described for known compounds.

Compounds of formula (IIb), equivalent to compounds of formula (II) in which X is a carbon atom, may be prepared by conversion of the hydroxy group of compounds of formula (VIII) into a leaving group.

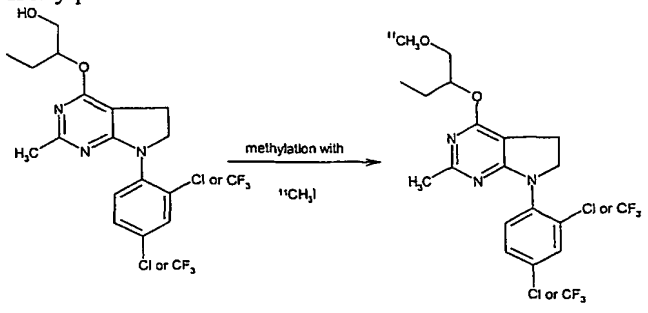


For example, the halogenation reaction may be carried out using conventional methods known in the art. Thus, e.g. the reaction may be carried out by treatment with $PO(Hal)_3$, wherein Hal is preferably chlorine.

The invention as herein described also includes isotopically-labeled compounds, which are identical to those falling within the scope of formulas I, Ia and Ib, , but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine, iodine, and chlorine, such as ^{3}H, ^{11}C, ^{14}C, ^{18}F, ^{123}I and ^{125}I. Compounds of the present invention and pharmaceutically acceptable salts of said compounds that contain the aforementioned isotopes and/or other isotopes of other atoms are within the scope of the present invention. Isotopically-labeled compounds of the present invention, for example those into which radioactive isotopes such as ^{3}H, ^{14}C are incorporated, are useful in drug and/or substrate tissue distribution assays. Tritiated, i.e., ^{3}H, and carbon-14, i.e., ^{14}C, isotopes are particularly preferred for their ease of preparation and detectability. ^{11}C and ^{8}F isotopes are particularly useful in PET (positron emission tomography), and ^{125}I isotopes are particularly useful in SPECT (single photon emission computerized tomography), all useful in brain imaging. Further, substitution with heavier isotopes such as deuterium, i.e., ^{2}H, can afford certain therapeutic advantages resulting from greater metabolic stability, for example increased *in vivo* half-life or reduced dosage requirements and, hence, may be preferred in some circumstances. Isotopically labeled compounds of this invention can generally be prepared by carrying out the procedures disclosed in the Schemes and/or in the Examples below, by substituting a readily available isotopically labeled reagent for a non-isotopically labeled reagent.

In another aspect of the present invention, the compounds of formula (I) in which R_2 represents $-CHR_6R_7$, wherein R_6 or R_7 are defined as before and are substitueted by an isotopically labeled C1-6 alkoxy group, preferably an isotopically labeled methoxy group, may be very useful for the scope outlined before.

In particular, the compounds (1-9) and (1-12), whose preparation is reported in Example 1, show a good activity and may be easily prepared in a radiolabeled form as described above. These radiolabeled compounds may be easily prepared according to the following process, starting from the hydroxy precursors.



-Cl derivative: compound (1-10) (1-9a)

-CF_3 derivative: compound (1-16) (1-12a)

the Alzheimer's type, with early or late onset, with depressed mood; vascular dementia with depressed mood; mood disorders induced by alcohol, amphetamines, cocaine, hallucinogens, inhalants, opioids, phencyclidine, sedatives, hypnotics, anxiolytics and other substances; schizoaffective disorder of the depressed type; and adjustment disorder with depressed mood. Major depressive disorders may also result from a general medical condition including, but not limited to, myocardial infarction, diabetes, miscarriage or abortion, etc.

Compounds of the invention are useful as analgesics. In particular they are useful in the treatment of traumatic pain such as postoperative pain; traumatic avulsion pain such as brachial plexus; chronic pain such as arthritic pain such as occurring in osteo-, rheumatoid or psoriatic arthritis; neuropathic pain such as post-herpetic neuralgia, trigeminal neuralgia, segmental or intercostal neuralgia, fibromyalgia, causalgia, peripheral neuropathy, diabetic neuropathy, chemotherapy-induced neuropathy, AIDS related neuropathy, occipital neuralgia, geniculate neuralgia, glossopharyngeal neuralgia, reflex sympathetic dystrophy, phantom limb pain; various forms of headache such as migraine, acute or chronic tension headache, temporomandibular pain, maxillary sinus pain, cluster headache; odontalgia; cancer pain; pain of visceral origin; gastrointestinal pain; nerve entrapment pain; sport's injury pain; dysmennorrhoea; menstrual pain; meningitis; arachnoiditis; musculoskeletal pain; low back pain e.g. spinal stenosis; prolapsed disc; sciatica; angina; ankylosing spondyolitis; gout; burns; scar pain; itch; and thalamic pain such as post stroke thalamic pain.

Compounds of the invention are also useful for the treatment of dysfunction of appetite and food intake and in circumstances such as anorexia, anorexia nervosa and bulimia.

Compounds of the invention are also useful in the treatment of sleep disorders including dysomnia, insomnia, sleep apnea, narcolepsy, and circadian ritmic disorders.

Compounds of the invention are also useful in the treatment or prevention of cognitive disorders. Cognitive disorders include dementia, amnestic disorders and cognitive disorders not otherwise specified.

Furthermore compounds of the invention are also useful as memory and/or cognition enhancers in healthy humans with no cognitive and/or memory deficit.

Compounds of the invention are also useful in the treatment of tolerance to and dependence on a number of substances. For example, they are useful in the treatment of dependence on nicotine, alcohol, caffeine, phencyclidine (phencyclidine like compounds), or in the treatment of tolerance to and dependence on opiates (e.g. cannabis, heroin, morphine) or benzodiazepines; in the treatment of cocaine, sedative ipnotic, amphetamine or amphetamine-related drugs (e.g. dextroamphetamine, methylamphetamine) addiction or a combination thereof.

The invention therefore provides a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof for use in therapy, in particular in human medicine.

There is also provided as a further aspect of the invention the use of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof in the preparation of a medicament for use in the treatment of conditions mediated by CRF.

In an alternative or further aspect there is provided a method for the treatment of a mammal, including man, in particular in the treatment of condition mediated by CRF, comprising administration of an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt or a solvate thereof.

It will be appreciated that reference to treatment is intended to include prophylaxis as well as the alleviation of established symptoms.
Compounds of formula (I) may be administered as the raw chemical but the active ingredient is preferably presented as a pharmaceutical formulation.

Accordingly, the invention also provides a pharmaceutical composition which comprises at least one compound of formula (I) or a pharmaceutically acceptable salt thereof and formulated for administration by any convenient route. Such compositions are preferably in a form adapted for use in medicine, in particular human medicine, and can conveniently be formulated in a conventional manner using one or more pharmaceutically acceptable carriers or excipients.

Thus compounds of formula (I) may be formulated for oral, buccal, parenteral, topical (including ophthalmic and nasal), depot or rectal administration or in a form suitable for administration by inhalation or insufflation (either through the mouth or nose).

For oral administration, the pharmaceutical compositions may take the form of, for example, tablets or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g. pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g. lactose, microcrystalline cellulose or calcium hydrogen phosphate); lubricants (e.g. magnesium stearate, talc or silica); disintegrants (e.g. potato starch or sodium starch glycollate); or wetting agents (e.g. sodium lauryl sulphate). The tablets may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents (e.g. sorbitol syrup, cellulose derivatives or hydrogenated edible fats); emulsifying agents (e.g. lecithin or acacia); non-aqueous vehicles (e.g. almond oil, oily esters, ethyl alcohol or fractionated vegetable oils); and preservatives

A proposed dose of the compounds of the invention is 1 to about 1000mg per day. It will be appreciated that it may be necessary to make routine variations to the dosage, depending on the age and condition of the patient and the precise dosage will be ultimately at the discretion of the attendant physician or veterinarian. The dosage will also depend on the route of administration and the particular compound selected.

Thus for parenteral administration a daily dose will typically be in the range of 1 to about 100 mg, preferably 1 to 80 mg per day. For oral administration a daily dose will typically be within the range 1 to 300 mg e.g. 1 to 100 mg.

EXAMPLES

In the Intermediates and Examples unless otherwise stated:

Melting points (m.p.) were determined on a Gallenkamp m.p. apparatus and are uncorrected. All temperatures refers to °C. Infrared spectra were measured on a FT-IR instrument. Proton Magnetic Resonance (^{1}H-NMR) spectra were recorded at 400 MHz, chemical shifts are reported in ppm downfield (d) from Me_4Si, used as internal standard, and are assigned as singlets (s), doublets (d), doublets of doublets (dd), triplets (t), quartets (q) or multiplets (m). Column chromathography was carried out over silica gel (Merck AG Darmstaadt, Germany). The following abbreviations are used in text: EtOAc = ethyl acetate, cHex = cyclohexane, CH_2Cl_2 = dichloromethane, Et_2O = dietyl ether, DMF = N,N'-dimethylformamide, DIPEA=N,N-diisopropylethylamine MeOH = methanol, Et_3N = triethylamine, TFA = trifluoroacetic acid, THF = tetrahydrofuran, DIBAL-H=diisobutylaluminium hydride, DMAP=dimethylaminopyridine, LHMDS= lithiumhexamethyldisilazane; Tlc refers to thin layer chromatography on silica plates, and dried refers to a solution dried over anhydrous sodium sulphate; r.t. (RT) refers to room temperature.

Intermediate 1

5-Allyl-4,6-dihydroxy-2-methyl-pyrimidine

Sodium (2 g) was added portionwise to anh. MeOH (100 ml), at 0°C, under N_2. After consumption of metallic sodium, acetamidine hydrochloride (8.4 g) was added. After 10 min. of stirring the precipitated NaCl was filtered off. Diethyl-allyl-malonate (6 ml) was added to the solution of free acetamidine and the mixture was stirred at r.t. for 2 days. The reaction mixture was concentrated and then neutralized with concentrated hydrochloric acid, filtered to obtain the title compound as a white solid (4.25 g).

NMR (^{1}H, DMSO-d_6): δ 11.61 (bs, 2H), 5.75 (m, 1H), 4.92 (m, 1H), 4.84 (m, 1H), 2.94 (d, 2H), 2.19 (s, 3H).

MS (*m/z*): 166 $[M]^+$.

Intermediate 2

5-Allyl-4,6-dichloro-2-methyl-pyrimidine

extracted with CH_2Cl_2 (3x10 ml). The combined organic extracts were dried over anh. Na_2SO_4, filtered and concentrated to dryness *in vacuo*. The crude product was purified by flash chromatography (silica gel, cHex/EtOAc 85:15) to give the title compound as white solid (120 mg).

NMR (^1H, $CDCl_3$): δ 7.49 (d, 1H), 7.37 (d, 1H), 7.23 (dd, 1H), 3.93 (q, 2H), 3.05 (t, 2H), 2.59 (s, 3H), 1.89 (bs, 1H), 1.45 (s, 9H).

IR (nujol, cm^{-1}): 3430, 1717.

MS (*m/z*): 432 $[MH]^+$, 3Cl; 454 $[MH+Na]^+$, 332 $[MH-Boc+H]^+$

Intermediate 6

Methanesulfonic acid 2-{4-*tert*-butoxycarbonyl(2,4-dichloro-phenyl)amino]-6-chloro-2-methyl-pyrimidin-5-yl}ethyl ester

To a solution of intermediate 5 (337 mg) in anh. CH_2Cl_2 (15 ml), at r.t, under N_2, was added Et_3N (545µl) and CH_3SO_2Cl (120 µl). The reaction was stirred at r.t. for 18 hr. Water (15 ml) and EtOAc (15ml) were added, the phases were separated and the aqueous layer was extracted with additional EtOAc (2x15 ml). The combined organic extracts were washed with H_2O (20 ml), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography (silica gel, cHex/EtOAc 75:25) to give the title compound as a white foam (327 mg).

NMR (^1H, $CDCl_3$): δ 7.49 (d, 1H), 7.34 (d, 1H), 7.26 (m, 1H), 4.52 (t, 2H), 3.24 (t, 2H), 2.98 (s, 3H), 2.58 (s, 3H), 1.45 (s, 9H).

MS (*m/z*): 510 $[MH]^+$, 3Cl; 532 $[MH+Na]^+$, 454 $[MH-tBu+H]^+$, 410 $[MH-Boc+H]^+$

Intermediate 7

Methanesulfonic acid 2-[4-chloro-6-(2,4-dichloro-phenylamino)-2-methyl-pyrimidin-5-yl]-ethyl ester

A solution of intermediate 6 (327 mg) in 20% TFA in CH_2Cl_2 (10 ml) was stirred at r.t. for 2 hr. The solvent was removed *in vacuo* and the residue was partitionned between EtOAc (10 ml) and sat. aq. $NaHCO_3$ (10 ml), and the layers were separated. The aqueous layer was extracted with EtOAc (3x10 ml), and the combined organic extracts were dried over Na_2SO_4, filtered and concentrated to dryness *in vacuo* to dobtain the title compound as white solid (224 mg).

NMR (^1H, $CDCl_3$): δ 8.39 (d, 1H), 7.49 (d, 1H), 7.44 (bs, 1H), 7.34 (dd, 1H), 4.56 (t, 2H), 3.28 (t, 2H), 3.03 (s, 3H), 2.61 (s, 3H).

MS (*m/z*): 410 $[MH]^+$, 3Cl.

Intermediate 8

4-Chloro-7-(2,4-dichloro-phenyl)-2-methyl-6,7-dihydro-5*H*-pyrrolo[2,3-*d*] pyrimidine

To a solution of intermediate 7 (224 m) in anh. THF (10 ml) was added, at r.t., under N_2, NaH (95% mineral oil, 20 mg). The reaction was stirred for 2 hr at r.t.. The solution was diluted with water (10 ml) and extracted with EtOAc (2x15 ml). The combined organic extracts were dried over anh. Na_2SO_4, filtered and concentrated to dryness *in vacuo*. The

evaporated to dryness *in vacuo*. The crude product was purified by flash chromatography (silica gel, cHex/EtOAc 9:1) to give the title compound as white solid (385 mg).
NMR (^{1}H, $CDCl_3$): δ 7.96 (bs, 1H), 7.86 (bd, 1H), 7.74 (d, 1H), 4.13-4.05 (m, 2H), 3.07 (td, 2H), 2.49 (s, 3H), 2.21 (bs, 1H), 1.41 (s, 9H).
IR (nujol, cm^{-1}): 1724, 1602.
MS (*m/z*): 500 $[MH]^+$; 444 $[MH\text{-}tBu+H]^+$; 400 $[MH\text{-}Boc+H]^+$.

Intermediate 12
Methanesulfonic acid 2-[4-(2,4-bis-trifluoromethyl-phenylamino)-6-chloro-2-methyl-pyrimidin-5-yl]-ethyl ester
To a solution of intermediate 11 (385 mg) in anh. CH_2Cl_2 (5 ml), at r.t, under N_2, were added Et_3N (540µl) and CH_3SO_2Cl (120µl). The reaction mixture was stirred at r.t. for 18 hr. Water (15 ml) and CH_2Cl_2 (15ml) were added and the phases were separated. The aqueous layer was extracted with CH_2Cl_2 (2x15 ml). The combined organic extracts were dried over Na_2SO_4, the solids filtered and the solvent evaporated *in vacuo*.
A solution of the crude product in 20% TFA/CH_2Cl_2 (4ml) was stirred at r.t. for 2 hr. The solvent was removed *in vacuo* and the residue was redissolved in EtOAc (10 ml) and sat. aq. $NaHCO_3$ (10 ml). The phases were separated and the aqueous layer was extracted EtOAc (3x10 ml). The combined organic extracts were dried over Na_2SO_4, the solids were filtered and the solvent evaporated to dryness *in vacuo* to deliver the title compound as a yellow solid (322 mg).
NMR (^{1}H, $CDCl_3$): δ 9.09 (bs, 1H), 8.12 (d, 1H), 8.09 (s, 1H), 7.74 (d, 1H), 4.36 (t, 2H), 3.23 (t, 2H), 3.15 (s, 3H), 2.19 (s, 3H).
IR ($CDCl_3$, cm^{-1}): 1346, 1177
MS (*m/z*): 478$[MH]^+$.

Intermediate 13
7-(2,4-Bis-trifluoromethyl-phenyl)-4-chloro-2-methyl-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidine
To a solution of intermediate 12 (320mg) in anh. THF (8 ml) was added, at r.t., under N_2, NaH (80% mineral oil, 30 mg). The reaction mixture was stirred for 2 hr at 60°C. It was then diluted with water (10 ml) and extracted with EtOAc (2x15 ml). The combined organic extracts were dried over anh. Na_2SO_4, the solids were filtered and the solvent evaporated to dryness *in vacuo*. The crude product was purified by flash chromatography (silica gel, cHex/EtOAc 90:10) to give the title compound as a white solid (154 mg).

Alternatively, intermediate 13 can be prepared from intermediate 24 as follows:
To a solution of intermediate 24 (514 mg, 1.29 mmol) in anh. CH_2Cl_2 (20 mL), at 0°C, under N_2, were added Et_3N (712 µL, 4 eq)) and mesyl chloride (197 µL, 2 eq) and the reaction mixture was stirred at r.t. for 18 hr. Water (20 mL) was then added and the phases were separated. The aqueous layer was extracted with CH_2Cl_2 (2x20 mL) and the combined organic extracts were dried over anh. Na_2SO_4. The solids were filtered and the solvent was

Intermediate 17

1-Trityloxy-butan-2-ol

To a solution of 1,2-butandiol (2 g) in anh. pyridine (15 mL) was added triphenylmethyl chloride (8 g). The dark reaction mixture was heated at 100°C for 8 hr and stirred at r.t. for 18 hr. The mixture was then poured in EtOAc/H_2O, the phases were separated and the organic layer was washed with sat. aq. NaCl and dried over Na_2SO_4. The solids were filtered and the solvent evaporated. The residual pyiridine was eliminated by filtration through a pad of silica gel (cHex/EtOAc 8:2). The solvent was evaporated and the residue was purified by flash chromatography (silica gel, cHex/EtOAc 95:5) to give the title compound as a yellow oil (2.67 g).

NMR (^{1}H, $CDCl_3$): δ 7.42 (m, 6H),7.2 (m, 9H), 3.67 (q, 1H), 3.18 (q, 1H), 3 (q, 1H), 2.6 (d, 1H), 1.42 (q, 2H), 0.85 (t, 3H).

MS (*m/z*): 332$[MH]^+$.

Intermediate 18

7-(2,4-Dichloro-phenyl)-2-methyl-4-(1-trityloxymethyl-propoxy)-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidine

To a solution of intermediate 17 (180 mg) in anh. *N*-methyl pyrrolidone (1ml), at r.t., under N_2, was added NaH 80%/oil (17 mg) and the reaction mixture was stirred at r.t. for 30 min. Intermediate 8 (80 mg) was then added and the reaction mixture was heated at 100 °C (screw cap vial) for 8 hr. It was then cooled down to r.t. and poured into CH_2Cl_2/H_2O. The phases were separated, the aqueous layer was extracted with CH_2Cl_2 (2x10 mL) and the combined organic extracts were dried over Na_2SO_4. The solids were filtered and the solvent evaporated to dryness *in vacuo*. The residue was purified by flash chromatography (silica gel cHex/EtOAc 9:1) to give the title compound as a clear oil (50 mg).

NMR (^{1}H,$CDCl_3$): δ 7.7-7.2 (m, 18H), 5.5 (m, 1H), 3.96 (t, 2H), 3.3 (q, 1H), 3.15 (q, 1H), 3.05 (t, 2H), 2.4 (s, 3H), 1.65 (m, 2H), 0.8 (t, 3H) .

MS (*m/z*): 610$[MH]^+$

Intermediate 19

2-[7-(2,4-Dichloro-phenyl)-2-methyl-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-4-yloxy]-butan-1-ol

A solution of intermediate 18 (8 mg) in EtOH (1 mL) and TFA (0.5 mL) was stirred at r.t. for 48 hr. The solvents were then evaporated, the residue taken up in CH_2Cl_2 and washed with H_2O (3x10 mL) to eliminate the residual acid. The organic layer was dried over Na_2SO_4, the solids were filtered and the solvent evaporated. The crude compound was purified by flash chromatography (silica gel cHex/EtOAc 9:1 → 8:2) to give the title compound (5 mg) as a clear oil.

MS (*m/z*): 368 $[MH]^+$.

NMR (^{1}H, DMSO-d_6): d 7.46 (d, 1H), 7.33 (d, 1H), 7.28 (dd, 1H), 4.87 (m, 1H), 3.99 (m, 2H), 3.85 (m, 2H), 3.09 (m, 2H), 2.38 (s, 3H), 1.69 (m, 2H), 1.03 (t, 3H).

(2,4-Bis-trifluoromethyl-phenyl)-{5-[2-(*tert*-butyl-dimethyl-silanoxy)-ethyl]-6-chloro-2-methyl-pyrimidin-4-yl}-amine

To a solution of 2,4-bis-trifluoromethyl-aniline (984 µL, 1 eq) in anh. DMF (15 mL), at 0°C, under N_2, was added NaH 80%/oil (400 mg, 2.2 eq). The reaction mixture was stirred at 0°C for 30 min and was then added to a solution of intermediate 22 (2 g, 6 mmol) in anh. DMF (15 mL) at r.t., under N_2. The reaction mixture was stirred at r.t. for 30 min. The excess NaH was carefully destroyed with sat.aq. NaCl and the reaction mixture was diluted with EtOAc. The phases were separated, the organic layer was washed with sat.aq. NaCl (2x30 mL) and dried over anh. Na_2SO_4. The solids were filtered and the solvent evaporated. The crude compound was purified by flash chromatography (silica gel, cHex/EtOAc 95:5 → 90:10). The title compound was obtained as a clear oil (1.84 g, 56%).

NMR (^{1}H, $CDCl_3$): δ 8.61 (d, 1H), 8.04 (bs, 1H), 7.86 (s, 1H), 7.79 (d, 1H), 4.95 (t, 2H), 3.95 (t, 2H), 2.53 (s, 3H), 0.73 (s, 9H), -0.90 (s, 6H).

MS (*m/z*): 514 $[MH]^+$

Intermediate 24

2-[4-(2,4-Bis-trifluoromethyl-phenylamino)-6-chloro-2-methyl-pyrimidin-5-yl]-ethanol

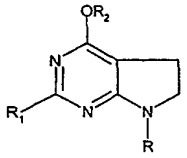
To a solution of intermediate 23 (1.84 g, 3.58 mmols) in anh. DMF (30 mL), at r.t., under N_2, was added $Et_3N{\cdot}3HF$ (2.4 mL, 3 eq). The reaction mixture was stirred at r.t. for 18 hr. It was then diluted with cold sat.aq. NaCl (50 mL) and extracted with EtOAc (3x50 mL). The combined organic extracts were dried over anh. Na_2SO_4. The solids were filtered and the solvent evaporated. The title compound was obtained as a clear oil (1.4 gr, 98%) and was used in the next step without further purification.

NMR (^{1}H, $CDCl_3$): δ 8.59 (bs, 1H), 8.22 (d, 1H), 7.84 (s, 1H), 7.75 (d, 1H), 4.06 (t, 2H), 3.01 (t, 2H), 2.50 (s, 3H)

MS (*m/z*): 400 $[MH]^+$

Example 1

Synthesis of representative compounds of structure (1a)



(1a)

7-(2,4-Dichlorophenyl)-4-(1-ethyl-propoxy)-2-methyl-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]-pyrimidine (1-1)

To a suspension of NaH 80%/oil (4 mg) in anh. DMF (300 µL), at r.t., under N_2, was added 3-pentanol (15.5 µL) and the reaction mixture was heated at 50°C for 15-20 min, or until a clear orange solution was obtained. Intermediate 8 (15 mg) was then added and the reaction mixture was heated at 100°C (screw cap vial) for 60 min. It was then cooled down to r.t. and the solvent was evaporated. The residue was taken-up in H_2O and the aqueous layer was extracted with CH_2Cl_2 (3x10 mL). The combined organic extracts were dried over Na_2SO_4,

at 60°C for 15 hr. It was then cooled down to r.t. and poured in CH_2Cl_2/H_2O. The phases were separated and the organic layer was dried over Na_2SO_4. The solids were filtered and the solvent was evaporated to yield the title compound as a white foam (12 mg).

7-(2,4-Dichlorophenyl)-4-(2-ethoxy-1-ethoxymethyl-ethoxy)-2-methyl-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidine (1-6)

To a suspension of NaH 80%/oil (4.0 mg) in anh. DMF (300 µl) at r.t., under N_2, was added 1,3-diethoxy-2-propanol (22.0 µl). The reaction mixture was stirred at 80°C for 30 min. Intermediate 8 (15 mg) was then added and the reaction mixture was heated at 110°C (screw cap vial) for 1hr. It was then cooled down to r.t. and poured into EtOAc. The organic layer was washed with sat. aq. NaCl (3x10 mL) and dried over Na_2SO_4. The solids were filtered and the solvent evaporated. The crude product was purified by flash chromatography (silica gel, CHex/EtOAc 96:4) to give the title compound as a colourless oil (12.0 mg).

7-(2,4-Bis-trifluoromethyl-phenyl)-4-(1-ethyl-propoxy)-2-methyl-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidine (1-7)

To a suspension of NaH 80 %/oil (4.8 mg) in anh. DMF (300 µl), at r.t., under N_2, was added pentan-3-ol (17 µl). The reaction mixture was stirred at 80°C for 15 min. Intermediate 13 (20 mg) was then added and the reaction mixture was heated at 110°C (screw cap vial) for 1h. It was then cooled down to r.t. and poured into EtOAc. The organic layer was washed with sat. aq. NaCl (3x10 mL) and dried over Na_2SO_4. The solids were filtered and the solvent evaporated. The crude product was purified by flash chromatography (silica gel, cHex/EtOAc 95:5) to give the title compound as a pale yellow solid (13.2 mg).

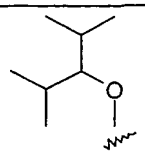
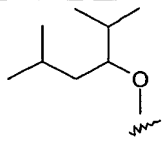
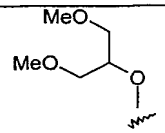
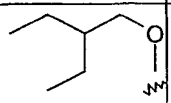
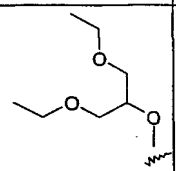
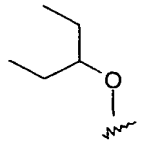
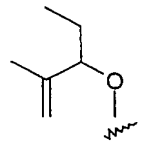
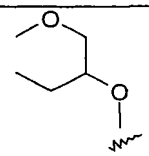
Example 1-1-13, 1-1-14 and 1-1-15 were prepared analogously, except that 2-trifluoromethyl-4-cyano-aniline, 2-chloro-3-amino-6-trifluoromethyl-pyridine and 2-cyano-4-trifluoromethyl-aniline were used respectively instead of 2,4-bis-trifluoromethyl-aniline in the production of intermediate 23

7-(2,4-Dichlorophenyl)-4-(1-ethyl-2-methyl-allyloxy)-2-methyl-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidine (1-8)

To a suspension of NaH 80%/oil (4.0 mg) in anh. DMF (300 µl) at r.t., under N_2, was added 2-methyl-1-penten-3-ol (15 mg). The reaction mixture was stirred at 80°C for 30 min. Intermediate 8 (15 mg) was then added and the reaction mixture was heated at 110°C (screw cap vial) for 1hr. It was then cooled down to r.t. and poured into EtOAc. The organic layer was washed with sat. aq. NaCl (3x10 mL) and dried over Na_2SO_4. The solids were filtered and the solvent evaporated. The crude product was purified by flash chromatography (silica gel, cHex/EtOAc 96:4) to give the title compound as colourless oil (7 mg).

7-(2,4-Dichlorophenyl)-4-(1-methoxymethyl-propoxy)-2-methyl-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidine (1-9)

To a suspension of NaH 80%/oil (4.0 mg) in anh. DMF (300 µl) at r.t., under N_2, was added 1-methoxy-butan-2-ol (15 mg). The reaction mixture was stirred at 80°C for 30 min.

1-2	2,4-dichlorophenyl	CH_3		NMR (^{1}H, $CDCl_3$): δ 7.46 (d, 1H), 7.40 (d, 1H), 7.27 (dd, 1H), 5.16 (t, 1H), 3.96 (t, 2H), 3.05 (t, 2H), 2.37 (s, 3H), 2.00 (m, 2H), 0.93 (d, 12H). MS (*m/z*): 394 $[MH]^+$ 2 Cl.
1-3	2,4-dichlorophenyl	CH_3		NMR (^{1}H, $CDCl_3$): δ 7.51 (bs, 1H), 7.38 (d, 1H), 7.33 (bd, 1H), 5.39 (m, 1H), 4.03 (bt, 2H), 3.11 (t, 2H), 2.58 (bs, 3H), 1.95, m, 1H), 1.68-1.55 (m, 2H), 1.35 (m, 1H), 0.95 (m, 12H). MS (*m/z*): 408 $[MH]^+$ 2 Cl.
1-4	2,4-dichlorophenyl	CH_3		NMR (^{1}H,): δ 7.47 (d, 1H), 7.35 (d, 1H), 7.28 (dd, 1H), 5.64 (m, 1H), 3.97 (t, 2H), 3.68 (m, 4H), 3.41 (s, 3H), 3.40 (s, 3H), 3.10 (t, 2H), 2.43 (s, 3H). MS (*m/z*): 398 $[MH]^+$ 2 Cl.
1-5	2,4-dichlorophenyl	CH_3		NMR (^{1}H,): δ . 7.46 (d, 1H), 7.37 (d, 1H), 7.27 (dd, 1H), 4.29 (d, 2H), 3.96 (t, 2H), 3.06 (t, 2H), 2.41 (s, 3H), 1.7-1.6 (m, 1H), 1.5-1.4(m, 4H), 0.95 (t, 6H). MS (*m/z*): 380 $[MH]^+$ 2 Cl.
1-6	2,4-dichlorophenyl	CH_3		NMR (^{1}H, $CDCl_3$): δ 7.42 (d, 1H), 7.31 (d, 1H), 7.23 (dd, 1H), 5.54 (m, 1H), 3.92 (t, 2H), 3.68 (d, 4H), 3.55 (m, 4H), 3.04 (t, 2H), 2.35 (s, 3H), 1.17 (t, 6H). MS (*m/z*): 426 $[MH]^+$.
1-7	2,4-bis-trifluoro-methyl-phenyl	CH_3		NMR (^{1}H, $CDCl_3$): δ 8.01 (s, 1H), 7.88 (d, 1H), 7.57 (d, 1H), 5.25 (bs, 1H), 3.97 (t, 2H), 3.10 (t, 2H), 2.46 (bs, 3H), 1.71 (m, 4H), 0.96 (t, 6H). MS (*m/z*): 434 $[MH]^+$.
1-8	2,4-dichlorophenyl	CH_3		NMR (^{1}H, $CDCl_3$): δ 7.46 (d, 1H), 7.36 (d, 1H), 7.28 (dd, 1H), 5.58 (bs, 1H), 5.02 (s, 1H), 4.91 (s, 1H), 3.98 (m, 2H), 3.08 (m, 2H), 2.41 (bs, 3H), 1.81 (m, 2H), 1.78 (s, 3H), 0.95 (t, 3H). MS (*m/z*): 378 $[MH]^+$.
1-9	2,4-dichlorophenyl	CH_3		NMR (^{1}H, $CDCl_3$): δ 7.46 (d, 1H), 7.36 (d, 1H), 7.28 (dd, 1H), 5.43 (m, 1H), 3.98 (m, 2H), 3.62 (dd, 1H), 3.56 (dd, 1H), 3.41 (s, 3H), 3.08 (m, 2H), 2.42 (s, 3H), 1.75 (m, 2H), 0.98 (t, 3H). MS (*m/z*): 382 $[MH]^+$.

CRF binding affinity has been determined in vitro by the compounds' ability to displace ^{125}I-oCRF and ^{125}I-Sauvagine for CRF1 and CRF2 SPA, respectively, from recombinant human CRF receptors expressed in Chinese Hamster Ovary (CHO) cell membranes. For membrane preparation, CHO cells from confluent T-flasks were collected in SPA buffer (HEPES/KOH 50mM, EDTA 2mM; $MgCl_2$ 10mM, pH 7.4.) in 50mL centrifuge tubes, homogenized with a Polytron and centrifuged (50'000g for 5min at 4°C: Beckman centrifuge with JA20 rotor). The pellet was resuspended, homogenized and centrifuged as before.

The SPA experiment has been carried out in Optiplate by the addition of 100 µL the reagent mixture to 1µL of compound dilution (100% DMSO solution) per well. The assay mixture was prepared by mixing SPA buffer, WGA SPA beads (2.5 mg/mL), BSA (1 mg/mL) and membranes (50 and 5 µg of protein/mL for CRF1 and CRF2 respectively) and 50 pM of radioligand.

The plate was incubated overnight (>18 hrs) at room temperature and read with the Packard Topcount with a WGA-SPA ^{125}I counting protocol.

Example 3
CRF functional assay

Compounds of the invention were characterised in a functional assay for the determination of their inhibitory effect. Human CRF-CHO cells were stimulated with CRF and the receptor activation was evaluated by measuring the accumulation of cAMP.

CHO cells from a confluent T-flask were resuspended with culture medium without G418 and dispensed in a 96-well plate, 25'000c/well, 100 µL/well and incubated overnight. After the incubation the medium was replaced with 100 µL of cAMP IBMX buffer warmed at 37°C (5mM KCl, 5mM $NaHCO_3$, 154mM NaCl, 5mM HEPES, 2.3mM $CaCl_2$, 1mM $MgCl_2$; 1g/L glucose, pH 7.4 additioned by 1mg/mL BSA and 1mM IBMX) and 1µL of antagonist dilution in neat DMSO. After 10 additional minutes of incubation at 37°C in a plate incubator without CO2, 1µL of agonist dilution in neat DMSO was added. As before, the plate was incubated for 10 minutes and then cAMP cellular content was measured by using the Amersham RPA 538 kit.

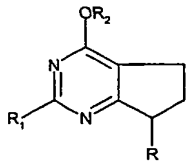
Example 4
General method for radiolabelling the compounds of formula (I)

Materials and Methods

Unless otherwise stated reagents may be obtained in analytical grade from commercial sources (Aldrich, Fluka, BDH, Phoenix, etc..) and may be used without carrying further purification.

Quality control of [^{11}C]derivatives may be performed on a Gilson high performance liquid chromatography (HPLC) system (305-307 pumps, 118 UV-detector) connected with a Bioscan Flow-Count. Data analyses of the chromatograms were carried out with Laura 3 software (LabLogic Systems Limited).

may be directed to any feature or combination of features described herein. They may take the form of product, composition, process, or use claims and may include, by way of example and without limitation, the following claims:



(Ib)

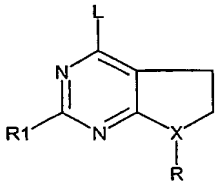
in which R, R_1, and R_2 are defined as in claim 1.

4. Compounds, according to any of claims from 1 to 3, wherein
R_1 is C1-C3 alkyl group or halo C1-C3 alkyl group.

5. Compounds, according to any of claims from 1 to 4, wherein
R is an aryl group selected from: 2,4-dichlorophenyl, 2-chloro-4-methylphenyl, 2-chloro-4-trifluoromethyl, 2-chloro-4-methoxyphenyl, 2,4-dimethylphenyl, 2-methyl-4-methoxyphenyl, 2-methyl-4-chlorophenyl, 2-methyl-4-trifluoromethyl, 2,4-dimethoxyphenyl, 2-methoxy-4-trifluoromethylphenyl, 2-methoxy-4-chlorophenyl, 3-methoxy-4-chlorophenyl, 2,5-dimethoxy-4-chlorophenyl, 2-methoxy-4-isopropylphenyl, 2-methoxy-4-trifluoromethylphenyl, 2-methoxy-4-isopropylphenyl, 2-methoxy-4-methylphenyl, 2-trifluoromethyl-4-chlorophenyl, 2,4-trifluoromethylphenyl, 2-trifluoromethyl-4-methylphenyl, 2-trifluoromethyl-4-methoxyphenyl, 2-bromo-4-isopropylphenyl, 4-methyl-6-dimethylaminopyridin-3-yl, 3,5-dichloro-pyridin-2-yl, 2,6-bismethoxy-pyridin-3-yl and 3-chloro-5-tricloromethyl-pyridin-2-yl.

6. A compound, according to any of claims from 1 to 5, selected in a group consisting from:

7. A process for the preparation of a compound of formula (I) as claimed in claim 1, which comprises the reaction of a compound of formula (II), wherein L is a leaving group,



(II)

with the alcohol compound (III) $HOCHR_{2a}R_{3a}$ wherein R_{2a} and R_{3a} have the meanings defined in claim 1 for R_2 and R_3 or are a group convertible thereto.

8. The use of a compound according to any of claims from 1 to 6, in the preparation of a medicament for use in the treatment of conditions mediated by CRF (corticotropin-releasing factor).

9. The use of a compound according to claim 8, in the preparation of a medicament for use in the treatment of depression and anxiety.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 02/02656

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D487/04 A61K31/519 A61K31/517 A61K51/00 A61P25/00
C07D239/70 C07D401/04 //(C07D487/04,239:00,209:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
WPI Data, EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 95 33750 A (PFIZER) 14 December 1995 (1995-12-14) cited in the application claims 1,13	1,8-10
A	example 20	1

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
18 November 2002	27/11/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Alfaro, Faus, I

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB 02/02656

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

see FURTHER INFORMATION sheet PCT/ISA/210

2. [X] Claims Nos.: 1-20 (all of them in part)
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.